REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claims Amendments:

Claims 7 and 24 have been canceled without prejudice or disclaimer. Applicants specifically reserve the right to file one or more continuation or divisional applications directed to the canceled subject matter.

Claim 1 has been amended to recite a method for transplanting a cellular composition, for which support can be found throughout the application, for example, at page 21, lines 11-17.

Claim 1 has also been amended to recite "an *ex vivo*" cellular composition, for which support can be found, for example, in the original claim 1 ("outside of a living organism").

Claim 1 has also been amended to recite "suspected of containing neoplastic cells", for which support can be found, for example, at page 13, lines 20-23.

Claim 1 has further been amended to recite that the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon. Support for this recitation can be found, for example, at page 20, lines 13-15; page 25, lines 24-26; page 26, lines 8-10; and page 26, lines 21-27.

Claim 22 has been amended to recite "prior to transplantation" to clarify the relationship of the steps, for which support can be found, for example, at page 20, lines 27-29.

New claims 26-33 have been added. Claim 26 corresponds to the original claim 21, further reciting that the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon. Support for this recitation can be found, for example, at page 20, lines 13-15; page 25, lines 24-26; page 26, lines 8-10; and page 26, lines 21-27.

Claims 27-33 correspond to the original claims 2-7 and 24, respectively.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to further pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Rejection Under 35 U.S.C. §112, Second Paragraph:

The rejection of claims 1-24 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite, has been obviated by amendments of claim 1. Specifically, "for future use" has been deleted from claim 1. In addition, the amended claim 1 recites a method of transplanting a cellular composition rather than a method of making a cellular composition.

The other rejected claims depend from claim 1, and likewise do not recite the terminology at issue.

Accordingly, this rejection is now moot. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. §112, First Paragraph:

The rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, as allegedly not being enabled with respect to "neoplastic cells" has been obviated as set forth below, with traversal.

Claim 1 has been amended to recite a group of neoplastic cells, including ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon. Thus, the amended claim 1 is directed to a method of transplanting a cellular composition, said method comprising the steps of:

(a) providing an *ex vivo* mixed cellular composition suspected of containing neoplastic cells, and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition, wherein the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon; and

(b) transplanting the treated cellular composition.

The Office Action indicates that the specification is enabling for neoplastic cells with hyperactive ras pathways, defective or deleted p53 alleles, and suppressed immune responsiveness (page 5, lines 5-7). Therefore, the amended claim 1, as well as its dependent claims 2-24, is enabled. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Nevertheless, Applicants wish to point out that claim 1 would have been allowable without reciting the specific group of neoplastic cells. As articulated in the response filed on December 5, 2002, it is not required to describe each and every species of a genus in

order to enable the genus. Since Applicants have disclosed a representative number of species within the genus of "neoplastic cells", the following claim is enabled:

A method of transplanting a cellular composition, said method comprising the steps of:

(a) providing an ex vivo mixed cellular composition suspected of containing neoplastic cells, and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition; and

(b) transplanting the treated cellular composition.

Applicants specifically reserve the right to prosecute the subject matter of the above claim in subsequent application(s).

Double Patenting

Claims 1-8 and 24 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 and 21 of copending application Serial No. 09/847,356 (Patent Application Publication No. 2002/0006398 A1). A terminal disclaimer, the Statement under 37 C.F.R. 3.73(b), and the prescribed fee are enclosed herewith to address this rejection. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §102:

The rejection of claims 1, 9-11, 13-15 and 24 under 35 U.S.C. §102(b) in view of McCormick (WO 94/18992 or U.S. Patent No. 5,801,029) is respectfully traversed as set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall* (CCPA 1978), 198 USPQ 344.

Claim 1, as amended, is directed to a method of transplanting a cellular composition, said method comprising the steps of:

(a) providing an *ex vivo* mixed cellular composition suspected of containing neoplastic cells, and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition, wherein the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon; and

(b) transplanting the treated cellular composition.

Claims 9-11, 13-15 and 24 all depend from claim 1 and thus contain all the claim elements recited above.

McCormick relates to methods of ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus with mutated E1A or E1B. With respect to the use of *ex vivo* compositions, which is required by the claimed invention, McCormick only teaches diagnostic methods (see, *e.g.*,column 16, lines 26-49 of U.S. Patent No. 5,801,029). Briefly, McCormick describes that a cell sample can be infected with a suitable adenovirus, and the cells in the cell sample that express a replication phenotype can be quantified to provide a measure of the amount of neoplastic cells in the sample. McCormick thus does not teach a method of transplantation.

In contrast, the present invention relates to a method of transplanting a cellular composition by first treating the composition with a virus, and then transplanting the treated composition. These claim elements are clearly not taught by McCormick.

Accordingly, McCormick does not teach each and every element of the claimed invention. Therefore, the requirement under 35 U.S.C. §102 is not met, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103:

A. The rejection of claims 2-6 and 8 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and U.S. Patent No. 5,801,029) in view of Lee et al. (U.S. Patent No. 6,136,307) is respectfully traversed for the reasons set forth below.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

This rejection does not meet the criteria required under 35 U.S.C. §103. Claim 2 is directed to a method of transplanting purged hematopoietic stem cells, which comprises the steps of:

(a) providing an *ex vivo* mixed cellular composition suspected of containing neoplastic cells, and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition, wherein the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon; and

(b) transplanting the treated cellular composition;

wherein the cellular composition comprises hematopoietic stem cells. Claims 3 and 4 depend from claim 2, further requiring that the hematopoietic stem cells be harvested from bone marrow and blood, respectively.

Both of the McCormick references relate to methods of ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus with mutated E1A or E1B. Nowhere do these references teach or suggest transplanting virus-treated cellular compositions, let alone hematopoietic stem cells. Similarly, Lee et al. teach methods of treating proliferative disorders, including hematopoietic neoplasms, with reovirus. However, Lee et al. do not specifically teach or suggest transplantation of purged compositions. Therefore, there is no teaching or suggestion in the references to modify the reference or to combine reference teachings to arrive at the inventions of claims 2-4.

Similarly, claims 5, 6 and 8 relate to methods of preparing cellular compositions that comprise tissues, organs, part thereof, cultured cells, semen or eggs. Again, none of the references teach or suggest a method of transplanting these cellular compositions, and there is no motivation to combine and/or modify the references to arrive at the claimed invention.

Accordingly, the requirement under 35 U.S.C. §103(a) is not satisfied, and Applicants respectfully request that this rejection be withdrawn.

B. The rejection of claim 7 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and U.S. Patent No. 5,801,029) in view of Lee et al. (U.S. Patent No. 6,136,307), and further in view of Bensinger (Bone Marrow Trans. 21: 113-115, 1998), is now moot since claim 7 has been canceled. Therefore, withdrawal of this rejection is respectfully requested.

Applicants further submit that the amended claim 1, which has incorporated an element from claim 7, is not obvious over McCormick in view of Lee et al. and Bensinger.

For the reasons set forth below, this rejection would fail to satisfy the three required criteria under 35 U.S.C. §103 for a *prima facie* case of obviousness.

As discussed above, claim 1 is directed to a method of transplanting a cellular composition that has been treated, *ex vivo*, with a virus capable of selectively killing neoplastic cells. The McCormick references teach methods of ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus with mutated E1A or E1B. Lee et al. teach methods of treating proliferative disorders with reovirus. Bensinger teaches that only limited data suggest that purging autografts has any favorable effect, and that there is a critical need for large, well-designed trials of purging techniques. As such, there is no motivation or suggestion to combine these references and modify the combined teachings to arrive at the claimed invention.

The Office Action states that the "ordinary skilled artisan would have been motivated to combine these teachings because the purging technique described by Bensinger is inefficient and complicated in achieving a goal that the methods of McCormick in view of Lee, et al., more efficiently achieve." (page 12, third paragraph of the Office Action of September 6, 2002; rejection maintained in the current Office Action). However, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01 (original emphasis); *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Here, even if Bensinger suggests the desirability of a better purging method, the references certainly do not suggest the desirability of the combination. The purging methods that Bensinger teaches, such as using drugs, chemicals, or antibodies specific for neoplastic cells, bear no similarity to the claimed invention. McCormick and Lee et al. do not specifically teach or suggest methods of transplantation, and there is no evidence that purging is a goal for either McCormick or Lee et al. Therefore, the references do not suggest the desirability of the combination.

Since the cited references do not meet the requirement under 35 U.S.C. §103, Applicants respectfully submit that this rejection would not apply to claim 1 or any other claim of this application.

C. The rejection of claim 12 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and U.S. Patent No. 5,801,029) in view of Strong et al. (EMBO J. 17(12):3351-3362, 1998) is respectfully traversed for the reasons set forth below.

Claim 12 relates to transplantation of an *ex vivo* cellular composition as described above, wherein the virus is mutated or modified such that the virus does not produce a gene product which inhibits double stranded RNA kinase (PKR).

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. However, these references do not teach or suggest transplantation of cellular compositions. Strong et al. teach the relationship of PKR and the ras pathway, but Strong et al. do not teach or suggest transplantation of virus-treated cells. Therefore, the references, either alone or in combination, do not teach or suggest all the elements of claim 12. In addition, there is no motivation or suggestion to combine and modify the references in the first place since none of the references relates, in any manner, to the use of a virus to purge a cellular composition.

Accordingly, withdrawal of this rejection is respectfully requested.

D. The rejection of claims 16-19 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and U.S. Patent No. 5,801,029) in view of Stodjl et al. (Nature Medicine 6(7):821-825, 2000) is respectfully traversed for the reasons set forth below.

Claims 16-19 relate to transplantation of cellular compositions as described above, wherein a virus and interferon are added to the cellular composition.

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. However, these references do not teach or suggest transplantation of cellular compositions. Stojdl et al. teach that the vesicular stomatitis virus (VSV) can be used along with interferon to treat interferon-non-responsive tumors. Like the McCormick references, Stojdl et al. do not teach or suggest transplantation of virus-treated compositions. Since none of the references teaches or suggests this required element, combining the references does not cure the deficiency. In addition, there is no motivation or suggestion to combine and modify the references in the first place since none of the references relates, in any manner, to the use of a virus to purge a cellular composition.

Accordingly, the requirement under 35 U.S.C. §103(a) is not satisfied, and Applicants respectfully request that this rejection be withdrawn.

E. The rejection of claims 22 and 23 under 35 U.S.C. §103(a) over McCormick (both WO 94/18992 and U.S. Patent No. 5,801,029) in view Stewart et al. (Bone Marrow Trans. 23:111-117, 1999) is respectfully traversed for the reasons set forth below.

Claims 22 and 23 relate to transplantation of virus-treated cellular compositions as described above, wherein the cellular composition is stored prior to transplantation, for example, in a DMSO solution.

The McCormick references, described above, suggest that certain adenovirus can be used for treating animals or diagnosis of cancer. Stewart et al. teach storage of stem cells in a DMSO solution. Since the McCormick references and Stewart et al. have completely unrelated teachings, there is simply no motivation or suggestion to combine these references and modify the teachings to arrive at the claimed invention.

Accordingly, the requirement under 35 U.S.C. §103 is not satisfied, and Applicants respectfully request the withdrawal of these rejections.

Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is invited to call the undersigned at (650) 622-2340.

Respectfully submitted,

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Attachment to Amendment dated May 15, 2003
Marked-up Copy
Claims 1 and 22

1. (Currently amended) A method of transplanting [preparing] a cellular composition [with a reduced amount of neoplastic cells by selectively removing neoplastic cells from a mixed cellular composition located outside of a living organism], said method comprising the steps of:

(a) providing [a] an *ex vivo* mixed cellular composition suspected of containing [which comprises] neoplastic cells and contacting the mixed cellular composition with a virus, wherein the virus is capable of selectively killing the neoplastic cells, under conditions which result in substantial killing of the neoplastic cells so as to selectively remove neoplastic cells from the composition, wherein the neoplastic cells are selected from the group consisting of ras-activated neoplastic cells, p53-deficient neoplastic cells, Rb-deficient neoplastic cells, and neoplastic cells that are not growth-inhibited by interferon; and

(b) [collecting] transplanting the treated cellular composition [for future use].

22. (Currently amended) The method of Claim 1 further comprising the step of storing the virus treated cellular composition prior to transplantation.